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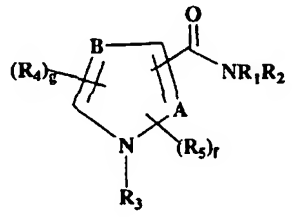
(54) Title: CANNABINOID RECEPTOR MODULATORS, THEIR PROCESSES OF PREPARATION, AND USE OF CANNABINOID RECEPTOR MODULATORS FOR TREATING RESPIRATORY AND NON-RESPIRATORY DISEASES



(I)

(57) Abstract: Use of a compound for treating a respiratory disease in a mammal wherein the compound is a cannabinoid receptor modulator is disclosed. Compounds useful as cannabinoid receptor modulators for treating respiratory and non-respiratory leukocyte-activation associated diseases comprise compounds of formula (I), in which A and B are nitrogen or carbon, provided only one of A and B is nitrogen; and R_1-R_6 are as defined in the specification, wherein R_2 with R_5 may form a ring, and/or two R_4 groups may form a six-membered aryl or heteroaryl ring, optionally having a substituent R_6 forming a ring with R_3.

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CANNABINOID RECEPTOR MODULATORS, THEIR PROCESSES OF PREPARATION, AND USE OF CANNABINOID RECEPTOR MODULATORS FOR TREATING RESPIRATORY AND NON-RESPIRATORY DISEASES

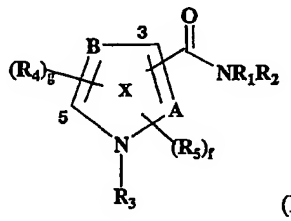
The present invention relates to compounds and compositions comprising cannabinoid receptor modulators, to processes for preparing such compounds and compositions, and to the use of cannabinoid receptor modulators in treating respiratory and non-respiratory diseases.

Delta-9 THC, the principle active component of marijuana, is a member of a large family of lipophilic compounds (*i.e.*, cannabinoids) that mediate physiological and psychotropic effects including immunosuppression, analgesia, inflammation, emesis, and intraocular pressure. Cannabinoids work through selective binding to G-protein coupled cannabinoid receptors. Two types of cannabinoid receptors have been cloned including CB1 (L.A. Matsuda *et al.* Nature, Vol. 346 [1990], pp. 561-564), and CB2 (S. Munro *et al*, Nature, Vol. 365 [1993], pp. 61-65). The CB1 receptor is found mainly on cells of the central nervous system, while the CB2 receptor is found mainly on cells of the peripheral nervous system including cells comprising the immune system such as lymphoid cells.

Compounds that reportedly bind to the cannabinoid G-protein receptors are disclosed in European Patent Documents Nos. EP 0570920 and EP 0444451; International Publications Nos. WO 97/29079, WO 99/02499, WO 98/41519, and WO 9412466; U.S. Patent Nos. 4,371,720, U.S. 5,081,122, U.S. 5,292,736, and U.S. 5,013,387; and French Patent No. FR 2735774, each of which is incorporated herein by reference.

Applicants have discovered that cannabinoid receptor modulators including cannabinoid receptor agonists are useful in treating respiratory disease, such as chronic pulmonary obstructive disorder, emphysema, asthma, and bronchitis. In one aspect of the invention, there is provided the use of cannabinoid receptor modulators in treating respiratory disease in a mammal comprising administering to said mammal an effective amount of at least one cannabinoid receptor modulator. Advantageously, the cannabinoid receptor modulator for this aspect of the invention is a CB2-receptor modulator.

The present invention is also directed to compounds and pharmaceutical compositions comprising at least one cannabinoid receptor modulator, and to the use of at least one such compound in treating respiratory and non-respiratory leukocyte activation-associated disorders, wherein the compound has the formula (I):



(I)

or a pharmaceutically-acceptable salt or hydrate thereof, in which:

A and B are selected from carbon and nitrogen so that ring X defines a pyrrole, pyrazole, or imidazole ring; wherein when A is nitrogen, the group -$C(=O)NR_1R_2$ is attached to atom C-3 and R_5 does not exist; and when A is carbon, one of the group -$C(=O)NR_1R_2$ and R_5 is attached to A and the other of -$C(=O)NR_1R_2$ and R_5 is attached to atom C-3; and when B is carbon, two R_4 groups attached to B and atom C-5, respectively, optionally form a fused 6-membered aryl or 6-membered heteroaryl having one heteroatom which is nitrogen, wherein said aryl or heteroaryl has three or four groups R_6;

f is 0 or 1;

g is 1 or 2;

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl,

heterocycloalkyl, cycloalkyl, aryl, and heterocyclo; or R_2 together with R_1 or R_5 forms a five or six membered heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy, or forms a heterocyclo with one of R_6;

R_4 is attached to atom C-5 and optionally B and at each occurrence independent of each other R_4 is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$; or when B is carbon, optionally two R_4 groups taken together form a six-membered aryl or heteroaryl having three or four R_6;

R_5 is attached to A or atom C-3 and is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkoxy, aryl, or heterocyclo; or R_5 together with R_2 forms a heterocyclo;

R_6 at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; and/or one R_6 group together with R_3 forms a heterocyclo;

R_8 and R_9 at each occurrence independent of each other R_8 and R_9 are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_8 and R_9 together form a three-to-eight membered heterocyclo; or R_8 together with R_{10} forms a three-to-eight membered heterocyclo; and

R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8; and u is 0, 1, 2 or 3.

According to another aspect of the invention, there are provided pharmaceutical compositions useful for treating respiratory disease comprising an effective amount of at least one cannabinoid receptor modulator according to formula (I) in a pharmaceutically-acceptable carrier or modulator. In a further aspect of the invention, there are provided compounds useful as cannabinoid receptor modulators and pharmaceutical compositions comprising such cannabinoid receptor modulators, wherein the compounds comprise selected compounds according to formula (I), as defined hereinafter. In a still further aspect of the invention, there is provided a process of preparing one or more intermediates to compounds of formula (I), and processes for preparing compounds of formula (I).

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two or three substituents selected from the group consisting of halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a, -SH, keto (=O), -C(=O)H, $-CO_2H$, $-C(=O)(R_a)$, $-CO_2(R_a)$, $-SO_3H$, $-S(O)_{0-2}(R_a)$, $-S(O)_2NR_aR_b$, $-C(=O)N(R_a)O(R_b)$, $-C(=O)N(R_a)_2$, $-OC(=O)R_a$, cycloalkyl, or aryl, wherein at each occurrence each of the groups R_a, R_b are independently selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_a and R_b taken together form a three-to-eight membered heterocyclo.

When the term "alkyl" is used to suffix another group, such as in "arylalkyl", "heterocycloalkyl" or cycloalkylalkyl," the term defines with more specifity at least one of the groups that a substituted alkyl will contain. In other words, in these instances the specifically-named groups are bonded directly through a substituted or unsubstituted alkyl chain as defined above. For example, an arylalkyl includes

benzyl, and a heterocycloalkyl includes ethyl-morpholino or any other straight or branched hydrocarbon chain of 1 to 12 carbon atoms having a substituted or unsubstituted heterocyclo as one of its substituents.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond. When reference is made to a substituted alkenyl, the alkenyl group will have one to three substituents as recited above for alkyl groups.

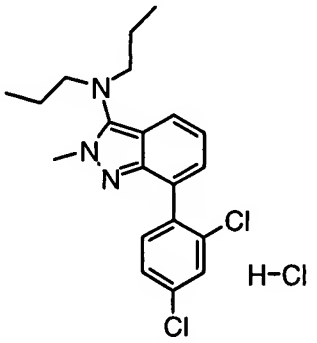
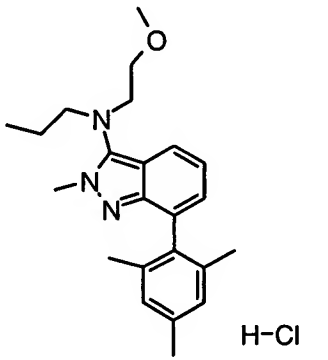
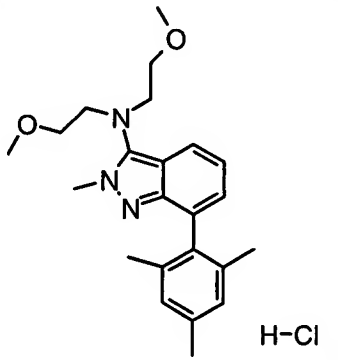
The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond. A "substituted alkynyl" is substituted with one to three substituents as recited above for alkyl groups.

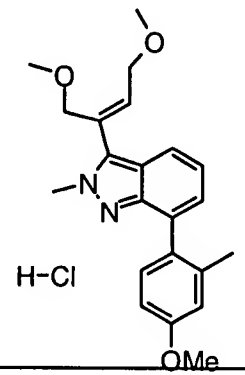
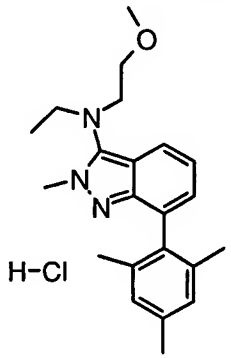
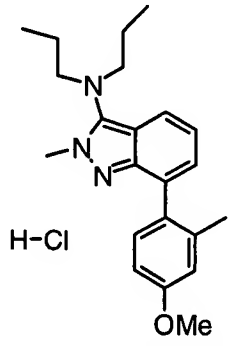
The term "alkylene" refers to a chain bridge of 1 to 5 carbon atoms connected by single bonds {*e.g.*, $-(CH_2)_x-$ wherein x is 1 to 5}, which may be branched with 1 to 3 lower alkyl groups.

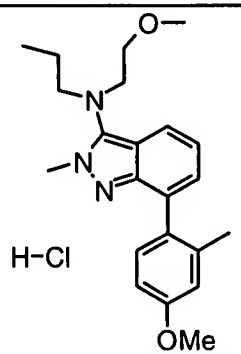
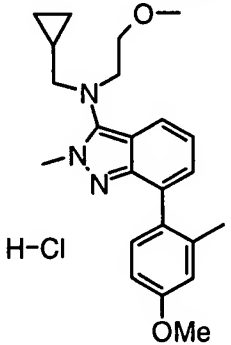
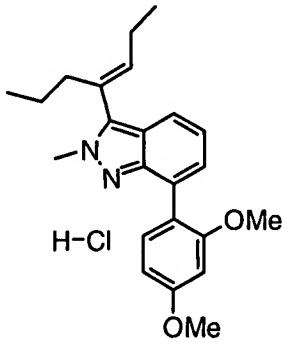
The term "alkenylene" refers to a chain bridge of 2 to 5 carbon atoms having one or two double bonds connected by single bonds and which may be branched with 1 to 3 lower alkyl groups. Exemplary alkenylene groups include -CH=CH-CH=CH-, $-CH_2$-CH=CH-, $-CH_2$-CH=CH-CH_2-, $-C(CH_3)_2CH$=CH- and $-CH(C_2H_5)$-CH=CH-.

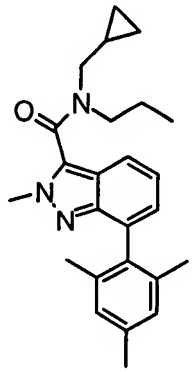
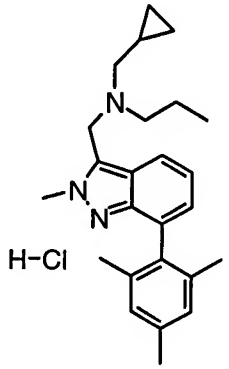
The term "alkynylene" refers to a chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be branched with 1 to 3 lower alkyl groups. Exemplary alkynylene groups include -C≡C-, $-CH_2$-C≡C-, $-CH(CH_3)$-C≡C- and -C≡C-$CH(C_2H_5)CH_2$-. When reference is made to a substituted alkylene, substituted alkenylene, or substituted alkynylene, these groups may have 1 to 3 substituents as defined above for alkyl groups.

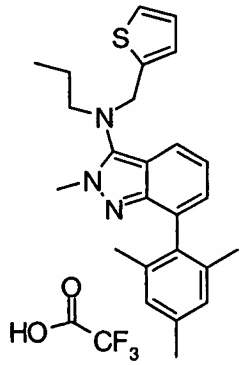
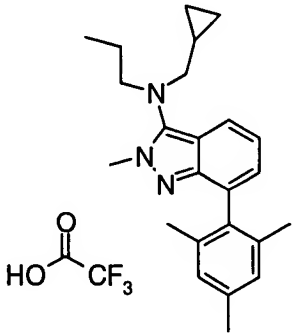
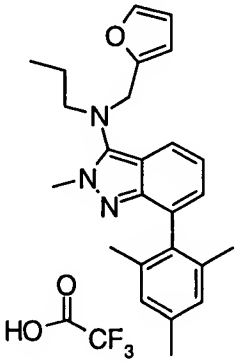
The term "alkoxy" refers to the group OR_o, wherein the group R_o is selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclo, substituted alkyl, heterocycloalkyl, substituted alkenyl, or substituted alkynyl.

RO4580011-001		[7-(2,4-Dichloro-phenyl)-2-methyl-2H-indazol-3-yl]-dipropyl-amine	6.8	8.2	153-157	376 (376)
RO4583820-001		(2-Methoxy-ethyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-yl]-propyl-amine	6.3	7.8	86-121	366 (366)
RO4583821-001		Bis-(2-methoxy-ethyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-yl]-amine	5.1		140-142	382 (382)

RO4593725-001		3-(3-Methoxy-1-methoxymethyl-propenyl)-7-(4-methoxy-2-methyl-phenyl)-2-methyl-2H-indazole hydrochloride	5.2	NA	oil	367 (367)
RO4593726-001		Ethyl-(2-methoxy-ethyl)-[2-methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-yl]-amine hydrochloride	6.1	7.8	142-146	352 (352)
RO4596760-001		[7-(4-Methoxy-2-methyl-phenyl)-2-methyl-2H-indazol-3-yl]-dipropyl-amine hydrochloride	6.1	7.5	60-70	352 (352)

RO4598093-001		(2-Methoxy-ethyl)-[7-(4-methoxy-2-methyl-phenyl)-2 methyl-2H-indazol-3-yl]-propyl-amine; hydrochloride	5.5	7		367 (367)
RO4598087-001		Cyclopropylmethyl-(2-methoxy-ethyl)-[7-(4-methoxy-2-methyl-phenyl)-2-methyl-2H-indazol-3-yl]-amine hydrochloride	5.5	7		379 (379)
RO4598733-001		7-(2,4-Dimethoxy-phenyl)-2-methyl-3-(1-propyl-but-1-enyl)-2H-indazole hydrochloride	6.2	NA		364 (364)

RO4597647-000		2-Methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazole-3-carboxylic acid cyclopropylmethyl-propyl-amide	7	8.4	112.5-113.8	390 (390)
RO4598086-001		Cyclopropylmethyl-[2-methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-ylmethyl]-propyl-amine hydrochloride	7.2	8.7	125.8-133.5	375 (375)

RO4598893-001		[2-Methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-yl] propyl-thiophen-2-ylmethyl-amine trifluoro-acetic acid salt	7.1	8.1		404 (404)
RO4598891-001		Cyclopropylmethyl-[2-methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-yl]-propyl-amine trifluoroacetic acid salt	7.3	8.8		362 (362)
RO4598888-001		Furan-2-ylmethyl-[2-methyl-7-(2,4,6-trimethyl-phenyl)-2H-indazol-3-yl]-propyl-amine trifluoroacetic acid salt	6.7	8		388 (388)

The term "amino" refers to $-NH_2$, and the term "aminoalkyl" refers to $-NR_cR_d$, wherein R_c and R_d are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, and $-C(=O)R_e$; or R_c and R_d are taken together to form a three-to-eight membered saturated or unsaturated heterocyclo ring which may have one to three substituents as defined below for heterocyclo groups. R_e is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo.

The term "alkylthio" refers to an alkyl or substituted alkyl group as defined above being further substituted with one of the groups –SH or $-SR_s$, wherein R_s is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo.

The term "alkylamide" refers to the group $-C(=O)NR_fR_g$, wherein R_f and R_g are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_f and R_g taken together form a three-to-eight membered heterocyclo.

The terms "ar" or "aryl" refer to aromatic cyclic groups, for example, 6 membered monocyclic, 10 membered bicyclic or 12 membered tricyclic ring systems, which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracenyl. Whenever reference is made to an aryl group (including without limitation in these definitions and in the claims), unless otherwise specifically indicated the aryl may have one to three substituents selected from the group consisting of R_a, halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a, -SH, -C(=O)H, $-CO_2H$, $-C(=O)(R_a)$, $-CO_2(R_a)$, $-SO_3H$, $-S(O)_{0-2}(R_a)$, $-S(O)_2NR_aR_b$, $-C(=O)N(R_a)O(R_b)$, $-C(=O)N(R_a)_2$, and $-OC(=O)R_a$ wherein at each occurrence each of the groups R_a, R_b are independently selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo, or taken together form a substituted or unsubstituted heterocyclo.

The term "cycloalkyl" refers to fully saturated and partially unsaturated cyclic hydrocarbon groups of 3 to 12 carbon atoms. Cycloalkyl groups may be bicyclic,

e.g., such as in bicycloheptane and bicyclooctane. Whenever reference is made to a cycloalkyl (including without limitation in these definitions and in the claims), unless otherwise specifically indicated the cycloalkyl may have one to three substituents selected from the group consisting of R_a, halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a, -SH, keto (=O), -C(=O)H, $-CO_2H$, $-C(=O)(R_a)$, $-CO_2(R_a)$, $-SO_3H$, $-S(O)_{0-2}(R_a)$, $-S(O)_2NR_aR_b$, $-C(=O)N(R_a)O(R_b)$, $-C(=O)N(R_a)_2$, and $-OC(=O)R_a$, wherein at each occurrence each of the groups R_a, R_b are independently selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo, or taken together form a heterocyclo.

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The terms "heterocycle", "heterocyclic" or "heterocyclo" refer to fully saturated or unsaturated, including aromatic (*i.e.* "heteroaryl") cyclic groups, for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one carbon atom-containing ring, and each ring of the heterocyclo is optionally substituted as defined below. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. Each ring of the heterocyclic group may have one or more (preferably one or two) substitutents selected from R_a, halo, cyano, nitro, amino, aminoalkyl, hydroxy, OR_a, -SH, keto (=O), -C(=O)H, $-CO_2H$, $-C(=O)(R_a)$, $-CO_2(R_a)$, $-SO_3H$, $-S(O)_{0-2}(R_a)$, $-S(O)_2NR_aR_b$, $-C(=O)N(R_a)O(R_b)$, $-C(=O)N(R_a)_2$, $-OC(=O)R_a$, wherein at each occurrence each of the groups R_a, R_b are independently selected from alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, monocyclic heterocycloalkyl or monocyclic heterocyclo, or taken together form a heterocyclo.

Exemplary monocyclic heterocyclic groups include pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl,

oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, triazolyl, triazinyl, and the like. The term "diazapine" refers to a heterocyclo having at least one seven atom ring with two nitrogen atoms in said seven atom ring.

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl, benzodioxolyl, benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl and the like.

Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "heteroaryl" refers to aromatic heterocyclic groups.

Exemplary heteroaryl groups include pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furyl, thienyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, triazinyl, and the like.

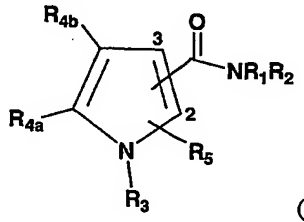
When reference is made to specifically-named heterocyclo, such as 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, thienyl, oxazole, and diazapine, and so forth, these rings may have one or more substituents as defined above for heterocyclo groups.

The term "unsaturated ring" includes partially or fully unsaturated and aromatic rings. When reference is made to an unsaturated heterocyclo, this means at least one ring of the heterocyclo is unsaturated (partially or fully), *i.e.*, in a bicyclic or tricyclic heterocyclo, only one ring of the heterocyclo need be at least partially unsaturated to comprise an unsaturated heterocyclo as defined herein.

Included within compounds of formula (I) are those compounds where A and B comprise carbon to define pyrrole-based compounds; where A is nitrogen and B is carbon to define pyrazole-based compounds; and where A is carbon and B is nitrogen to define imidazole-based compounds, as further defined below. One skilled in the field may make appropriate selections to provide stable compounds.

Pyrrole-Based Compounds

Compounds of formula (I) include pyrrole-based compounds useful as cannabinoid receptor modulators having formula (II), and pharmaceutically-acceptable salts thereof:



(II)

in which

one of R_5 and the group $-C(=O)NR_1R_2$ is attached to atom C-2 and the other of R_5 and the group $-C(=O)NR_1R_2$ is attached to atom C-3 of the pyrrole ring;

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, and heterocyclo; or R_2 together with R_1 forms a heterocyclo; or R_2 and R_5 form a heterocyclo and R_1 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, or alkoxy, or forms a heterocyclo with R_{4a};

R_{4a} and R_{4b} are (i) selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$; or (ii) taken together form a fused six-membered aryl or heteroaryl having three or four R_6;

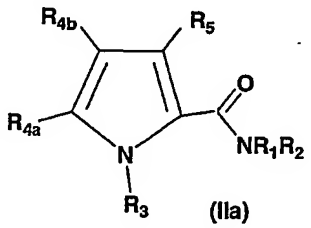
R_5 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, aryl, or heterocyclo; or R_5 is taken together with R_2 to form a heterocyclo;

R_6 at each occurrence is selected independently of each other R_6 from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; or one group R_6 forms a heterocyclo with R_3 and each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$;

R_8 and R_9 at each occurrence independent of each other R_8 and R_9 are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_8 and R_9 taken together form a three-to-eight membered heterocyclo; or R_8 together with R_{10} forms a three-to-eight membered heterocyclo; and

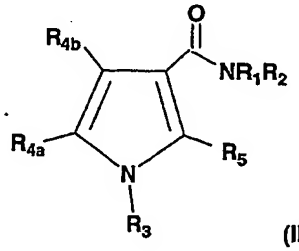
R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8, and u is 0, 1, 2 or 3.

Accordingly, included within compounds of formula (II) are cannabinoid receptor modulators comprising 2-carboxamide and 3-carboxamide pyrroles, *e.g.*, compounds having formula (IIa) or (IIb), and pharmaceutically-acceptable salts thereof:



(IIa)

or



(IIb)

wherein

R_1 and R_2 are (i) independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, aryl, cycloalkyl, and heterocyclo; or (ii) taken together form a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, or heterocyclo;

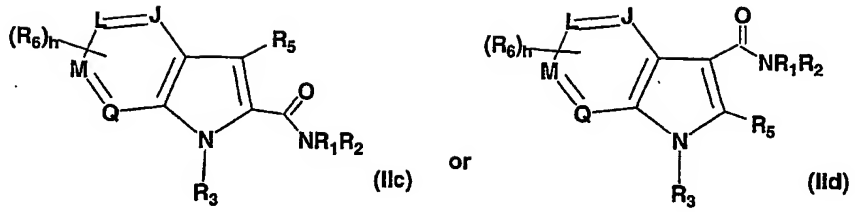
R_{4a} and R_{4b} are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$;

R_5 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkyny, alkoxy, aryl, or heterocyclo; and

R_{10} is alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and *u* is 0, 1, 2 or 3.

With respect to compounds of formulae (IIa) and (IIb) useful as cannabinoid receptor modulators, 3-carboxamide pyrroles are preferred. Additionally, advantageously R_1 is alkyl, substituted alkyl, heterocycloalkyl, aryl, cycloalkyl, or heterocyclo, and R_2 is hydrogen or C_{1-3}alkyl. R_3 is preferably heterocycloalkyl (particularly morpholinylethyl), and R_{4a} and R_{4b} are hydrogen, halogen, lower alkyl, or alkoxy (more preferably C_{1-5}alkoxy, OPh, or OBn). Also preferred are those carboxamide pyrroles where R_1 is $-CHR_{17}R_{18}$, wherein R_{17} and R_{18} are selected from substituted alkyl, $-CO_2$(alkyl), and alkylamide, or where R_{17} and R_{18} together form a cycloalkyl, an aryl, or a heterocyclo wherein said heterocyclo has sulfur or at least one of nitrogen and oxygen as its heteroatom(s).

Further included within compounds of formula (II) are compounds comprising bicyclic or tricyclic ringed systems having formula (IIc) or (IId), and pharmaceutically-acceptable salts thereof:

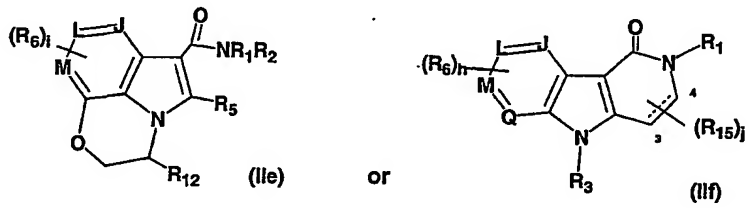


wherein J, L, M and Q are carbon or nitrogen, provided that only one of J, L, M and Q is nitrogen;

R_1, R_2, R_3, R_5 and R_6 are as defined above for compounds of formula (II), provided that when R_3 forms a ring with one of R_6, Q is carbon and R_2 is selected independently of R_5; and *h* is 3 or 4.

In compounds of formula (II), particularly (IIc) and (IId), when R_1 and R_2 together form a heterocyclo ring, advantageously said ring is unsaturated or is selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine. When R_1 and R_2 independently comprise heterocyclo, advantageously said heterocyclo has as its heteroatom or heteroatoms either (i) sulfur or, (ii) at least one of nitrogen and oxygen. For example, R_1 and R_2 may independently comprise pyridine, pyrazole, imidazole, tetrazole, oxazole, oxadiazole, thiophene, morpholine, and so forth. Advantageously, R_5 is not phenyl when attached to atom C-3 and at least one R_6 is alkoxy (preferably O-C_{1-5}alkyl, OPh, or OBn), and two R_6 groups are not simultaneously selected from amino and aminoalkyl.

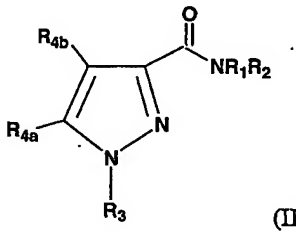
Further included within compounds of formula (IIc) and (IId) are compounds comprising tricyclic ringed systems having formula (IIe) or (IIf), respectively, and pharmaceutically-acceptable salts thereof:



wherein J, L, M, and Q are carbon or nitrogen, provided that only one of J, L, M and Q is nitrogen; R_1, R_2, R_3, R_5, R_6, R_8, R_9 and R_{10} are as defined above for compounds of formula (IIa) and (IIb); R_{12} and R_{15} selected independently of each other are hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, keto (=O), $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, or $-OC(=O)R_{10}$; *i* is 2 or 3; and *j* is 2 or 4. In compounds of formula (II), including (IIa) through (IIe), as they appear the groups J, L, M, and Q are preferably carbon; preferably R_1 is substituted alkyl and R_2 is hydrogen or C_{1-3}alkyl; R_3 and R_{12} are $-(CH_2)_n$-Z or $-O-(CH_2)_n$-Z, wherein Z is CH_3, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl, and *n* is 1 or 2; R_5 and R_{15} are hydrogen, halogen, methoxy, or lower alkyl; and each R_6 is hydrogen, alkoxy, lower alkyl, or halogen. More preferably, R_3 and R_{12} are morpholinylC_{1-3}alkyl.

Pyrazole-Based Compounds

Included within compounds of formula (I) are pyrazole-based compounds useful as cannabinoid receptor modulators having formula (III), and pharmaceutically-acceptable salts thereof:



(III)

in which

R_1 and R_2 are (i) independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, and heterocyclo; or (ii) taken together form a heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy; or forms a heterocyclo with R_{4a};

R_{4a} and R_{4b} are (i) selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo,

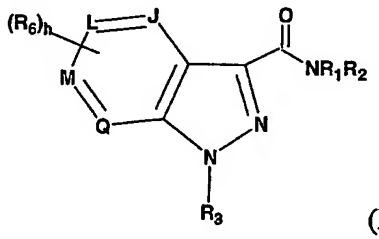
hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$; or (ii) taken together form a fused six-membered aryl or heteroaryl having three or four R_6;

R_6 at each occurrence is selected independently of each other R_6 from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; or one group R_6 forms a heterocyclo with R_3 and each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$;

R_8 and R_9 at each occurrence independent of each other are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_8 and R_9 taken together form a three-to-eight membered heterocyclo; or R_8 together with R_{10} forms a three-to-eight membered heterocyclo; and

R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, and *u* is 0, 1, 2 or 3.

Included within compounds of formula (III) are compounds comprising bicyclic ringed systems having formula (IIIa):



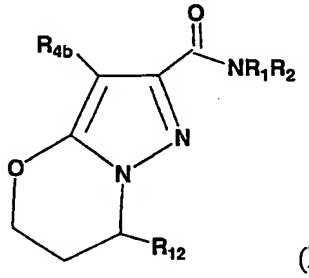
(IIIa)

wherein J, L, M and Q are carbon or nitrogen provided that only one of J, L, M and Q is nitrogen; R_1, R_2, R_8, R_9, and R_{10} are as defined above for compounds of

formula (III); R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, or alkoxy; R_6 at each occurrence is selected independently of each other R_6 from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; and *h* is 3 or 4;

Advantageously, in compounds of formula (IIIa), J, L, M, and Q are carbon. In compounds of formula (III) and (IIIa), when R_1 and R_2 together form a heterocyclo ring, advantageously said ring is unsaturated or is selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine; when R_1 and R_2 independently comprise heterocyclo, said heterocyclo has as its heteroatom or heteroatoms either (i) sulfur or, (ii) at least one of nitrogen and oxygen; and two R_6 groups are not simultaneously selected from amino and amino alkyl. Preferably, R_1 is substituted alkyl, and R_2 is hydrogen or C_{1-3}alkyl; R_3 is morpholinyl C_{1-3}alkyl; R_5 and R_{15} are hydrogen, halogen, methoxy, or lower alkyl; and each R_6 is selected from hydrogen, alkoxy, lower alkyl, or halogen.

Also included within compounds of formula (III) are compounds comprising bicyclic ringed systems having formula (IIIb):



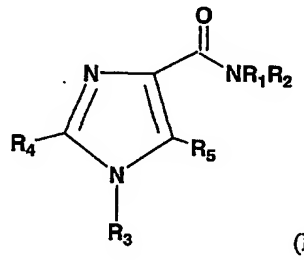
(IIIb)

wherein R_1, R_2, R_{4b}, R_8, R_9, and R_{10} are as defined above for compounds of formula (III); and R_{12} is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano,

halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$. Preferably, R_{12} is $(CH_2)_n$-Z, wherein Z is CH_3, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, aryl, cycloalkyl, or heterocyclo (preferably morpholinyl), and *n* is 1 or 2.

Imidazole-Based Compounds

Also included within compounds of formula (I) are imidazole-based compounds having formula (IV), or pharmaceutically-acceptable salts thereof:



(IV)

in which

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, aryl, cycloalkyl, and heterocyclo; or taken together form a heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, or heterocyclo;

R_4 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, or $S(O)_uR_{10}$;

R_5 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, aryl, or heteroaryl; and

R_{10} is alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, and *u* is 0, 1, 2 or 3.

In compounds of formula (IV), advantageously R_1 is substituted alkyl (more preferably $CHR_{17}R_{18}$, as defined herein); R_2 is hydrogen or $C_{1\text{-}3}$alkyl; R_3 is $-(CH_2)_n$-Z, wherein Z is CH_3, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, aryl, cycloalkyl, or

heterocyclo (preferably morpholinyl), and *n* is 1 or 2; and R_4 and R_5 are hydrogen, halogen, methoxy, or lower alkyl.

When reference is made herein to compounds of formula (I), such reference includes compounds of formulae (II), (III) and (IV). Compounds of formula (I) include salts, prodrugs and solvates. The term "salt(s)" as employed herein denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. Zwitterions (internal or inner salts) are included within the term "salt(s)" as used herein (and may be formed, for example, where the R substituents comprise an acid moiety such as a carboxyl group). Also included herein are quaternary ammonium salts such as alkylammonium salts. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, although other salts are contemplated as within the scope of the invention as they may be useful, for example, in isolation or purification steps employed during preparation. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates, methanesulfonates, 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates, undecanoates, and the like.

Exemplary basic salts (formed, for example, where the R substituents comprise an acidic moiety such as a carboxyl group) include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic

amines) such as benzathines, dicyclohexylamines, hydrabamines, N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. The basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.* methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.* dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (*e.g.* decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.* benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), or a salt and/or solvate thereof. Solvates of the compounds of formula (I) are preferably hydrates.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the R substituents of the compound of formula (I), including enantiomeric and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations.

According to the invention, cannabinoid receptor modulators, including compounds of formula (I), are typically employed as part of a pharmaceutical composition including a pharmaceutically-acceptable carrier for treating respiratory and/or non-respiratory diseases. The pharmaceutical compositions comprising at least one cannabinoid receptor modulator for treating respiratory disease and/or comprising compounds of formula (I), may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

The cannabinoid receptor modulators for treating respiratory disease and/or compounds of formula (I) may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally, such as in the form of suppositories; and in dosage unit formulations containing non-toxic, pharmaceutically-acceptable vehicles or diluents. The cannabinoid receptor modulators may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the cannabinoid receptor modulators, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The cannabinoid receptor modulators may also be administered in the form of liposomes.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The cannabinoid receptor modulators, including those for treating respiratory disease and/or compounds of formula (I), may also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the cannabinoid receptor modulators with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC),

maleic anhydride copolymer (*e.g.*, Gantrez), and agents to control release such as polyacrylic copolymer (*e.g.*, Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquefy and/or dissolve in the rectal cavity to release the drug.

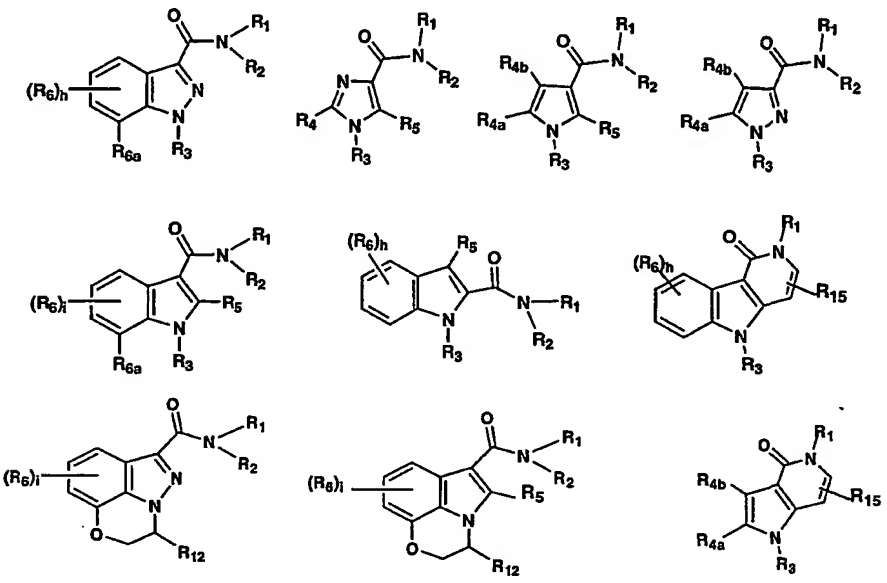
Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound employed in the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0.1 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the

like, subject to inflammatory, immunological, or respiratory cell-associated diseases and disorders.

Preferred Compounds

Particularly preferred compounds of the invention are compounds of formula (I) represented by the following structures:



wherein:

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or heterocyclo having at its heteroatom or heteratoms either sulfur or at least one of nitrogen and oxygen; or taken together form a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_3 and R_{12} are $-(CH_2)_n-Z$ or $-O-(CH_2)_n-Z$;

R_4, R_{4a}, R_{4b} and R_6 at each occurrence are selected from hydrogen, halogen, C_{1-6}alkyl, cyano, nitro, hydroxy, alkoxy, and phenyl;

R_5 is hydrogen, methyl, or ethyl;

R_{6a} is hydrogen or OR_8, wherein R_8 is hydrogen, C_{1-6}alkyl, aryl, or arylalkyl;

R_{15} is hydrogen, halogen, or alkyl;

Z is CH_3, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl,

h is 4;

i is 3; and

n is 1 or 2.

More preferred compounds are those represented by the above-referenced structures, wherein

R_1 is substituted alkyl or forms a heterocyclo with R_2 that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_2 is hydrogen, methyl, ethyl, or propyl, or forms a heterocyclo with R_1 that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_3 and R_{12} are $-(CH_2)_n$-Z;

R_4, R_{4a}, R_{4b} and R_6 at each occurrence are selected from hydrogen, halogen, C_{1-4}alkyl, hydroxy, and alkoxy;

R_5 is hydrogen or methyl;

R_{6a} is hydrogen or OR_8, wherein R_8 is hydrogen, C_{1-6}alkyl, aryl, or arylalkyl;

R_{15} is hydrogen, halogen, or C_{1-2}alkyl;

Z is heterocyclo;

n is 1 or 2;

h is 4; and

i is 3.

Further preferred compounds are those represented by the above-preferred structures, wherein

R_1 is $-CHR_{17}R_{18}$;

R_2 is hydrogen or methyl;

R_3 and R_{12} are $(CH_2)_n$-morpholinyl;

R_4, R_{4a}, R_{4b} and R_6 at each occurrence are selected from hydrogen, C_{1-4}alkyl, hydroxy, and alkoxy;

R_5 is hydrogen or methyl;

R_{6a} is hydrogen or OR_8, wherein R_8 is hydrogen, C_{1-5}alkyl, phenyl, or benzyl;

R_{15} is hydrogen, halogen, or C_{1-4}alkyl;

R_{17} and R_{18} are (i) selected independently from hydrogen and $-(CH_2)_s-(CR_{21}R_{22})_v-(CH_2)_t-W$; or (ii) R_{17} and R_{18} together form cycloalkyl, aryl, or heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;

W at each occurrence is selected independently from CH_3, alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$, $-NR_{19}(C=O)R_{20}$, aryl, cycloalkyl, and heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;

R_{19} and R_{20} are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo;

R_{21} and R_{22} are hydrogen, alkyl, hydroxy, or hydroxyalkyl;

h is 4;

i is 3;

n is 1 or 2;

s and *t* are 0, 1 or 2; and

v is 0 or 1.

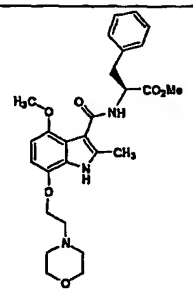
Also preferred are compounds as immediately defined above where R_{17} and R_{18} are (i) $-(CH_2)_s-W$, wherein W at each occurrence is selected from $-CH_3$, C_{1-4}alkylthio, C_{1-4}alkoxy, hydroxy, $-CO_2H$, $-CO_2C_{1-4}$alkyl, $-C(=O)N(C_{1-4}alkyl)_2$, $-C(=O)NH(C_{1-4}alkyl)$, $-C(=O)NH$(cycloalkyl), $-C(=O)H$, $-C(=O)NH_2$, $-C(=O)C_{1-4}$alkyl, $-C(=O)N(C_{1-4}alkyl)O(C_{1-4}alkyl)$, $-NH(C=O)C_{1-4}$alkyl, $-N(C_{1-4}alkyl)$(aryl), $-NH(C=O)$aryl, phenyl, imidazole, biphenyl, pyridine, pyrrolidine, thiophene, pyrazole, imidazole, tetrazole, oxazole, oxadiazole, and napthyl, wherein said group W is optionally substituted with one to four groups selected from C_{1-4}alkyl, hydroxy, halogen, C_{1-4}alkoxy, trifluoromethyl, amino, acetylamino, heterocyclo, benzyl, or

aryl; or (ii) taken together form a three-to-eight membered cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, aryl, cycloalkyl, and heterocyclo.

Methods of Preparation

Compounds of formula (I), cannabinoid receptor modulators illustrated in the Examples hereinafter, and intermediates for use in preparing the compounds of formula (I), may be prepared using the methods illustrated in the following Schemes A through N. Schemes A and B and G through J show schemes for preparing compounds of formula (I); schemes C through F show methods for preparing compounds useful as cannabinoid receptor modulators and as intermediates in preparing compounds of formula (I); schemes K through M describe in more detail inventive processes claimed herein for preparing compounds of formula (I); and scheme N illustrates a general procedure for Pd catalyzed indole cyclizations useful in preparing compounds of formula (I). For all of the schemes and compounds, the groups A, B, J, L, M, Q, R_1–R_6, R_{15}, and R_{16}, are as described above for a compound of formula I, unless otherwise indicated. Suitable selections may be made by one skilled in the field of appropriate groups for each of the groups X, R*, R', R", R_a, R_b or other groups generally referenced in these schemes. Solvents, temperatures, pressures, and other reaction conditions also may readily be selected by one of ordinary skill in the art. All documents cited are incorporated herein by reference in their entirety, and abbreviations that appear hereinafter are used in these schemes for ease of reference. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art.

The methods described herein may be carried out with starting materials and/or reagents in solution or alternatively, where appropriate, with one or more starting materials or reagents bound to a solid support {see (1) Thompson, L. A. and Ellman, J. A., Chemical Reviews, 96, pp. 555-600 (1996); (2) Terrett, N. K., *et al*, Tetrahedron, 51, pp. 8135-8173 (1995); (3) Gallop, M. A. *et al*, Journal of Medicinal Chemistry, 37, 1233-1251 (1994); (4) Gordon, E. M. *et al*, Journal of Medicinal Chemistry, 37, pp. 1385-1401 (1994); (5) Balkenhohl, F., *et al*, Angewandte Chemie International Edition in English, 35, pp. 2288-2337 (1996); (6) Balkenhohl, F. *et al*,

515		466.3/2.89(A)

CLAIMS

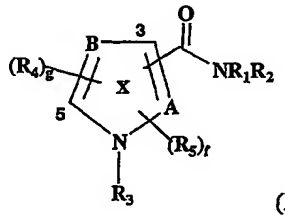
We claim:

1. A method for treating a respiratory disease in a mammal comprising administering to said mammal a therapeutically effective amount of at least one compound, or salt or hydrate thereof, in which the at least one compound is a cannabinoid receptor modulator.

2. The method of claim 1 in which the at least one compound, or salt or hydrate thereof, is a CB2 receptor modulator for blocking or substantially blocking the activation of lung epithelial cells to treat the respiratory disease.

3. The method of claim 2, in which the respiratory disease is selected from chronic pulmonary obstructive disorder, emphysema, asthma, and bronchitis.

4. A method of treating a respiratory or non-respiratory leukocyte-activation associated disease in a mammal comprising administering to said mammal an effective amount of at least one cannabinoid receptor modulator having the formula (I):



(I)

or a pharmaceutically acceptable salt or hydrate thereof, in which:

A and B are selected from carbon and nitrogen so that ring X defines a pyrrole, pyrazole, or imidazole ring; wherein when A is nitrogen, the group -$C(=O)NR_1R_2$ is attached to atom C-3 and R_5 does not exist; and when A is carbon, one of the group -$C(=O)NR_1R_2$ and R_5 is attached to A and the other of -$C(=O)NR_1R_2$ and R_5 is attached to atom C-3; and when B is carbon, two R_4 groups attached to B and atom C-5, respectively, optionally form a fused 6-

membered aryl or 6-membered heteroaryl having one heteroatom which is nitrogen, wherein said aryl or heteroaryl has three or four substituents R_6;

f is 0 or 1;

g is 1 or 2;

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, heterocyclo, or alkoxyalkyl; or R_2 together with R_1 or R_5 forms a five or six membered heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy; or forms a heterocyclo with one of R_6;

R_4 is attached to atom C-5 and optionally B and at each occurrence independent of each other R_4 is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, $NR_8C(=O)R_9$, and $S(O)_uR_{10}$; or when B is carbon, optionally two R_4 groups taken together form a six-membered aryl or heteroaryl having three or four R_6;

R_5 is attached to A or atom C-3 and is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkoxy, aryl, or heterocyclo; or R_5 together with R_2 forms a heterocyclo;

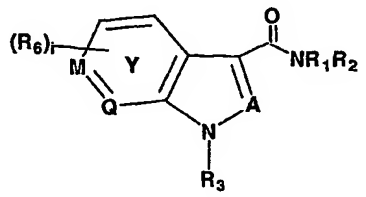
R_6 at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, substituted aryl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; and/or one R_6 group together with R_3 forms a heterocyclo;

R_8 and R_9 at each occurrence independent of each other R_8 and R_9 are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo; or R_8 and R_9 together form a three-to-eight membered heterocyclo; or R_8 together with R_{10} forms a three-to-eight membered heterocyclo; and

R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8; and

u is 0, 1, 2 or 3.

5. The method of claim 4, in which the cannabinoid receptor modulator has the formula:



or is a pharmaceutically acceptable salt or hydrate thereof, in which:

A is nitrogen or CR_5;

Q is nitrogen or CR_{6a} and M is carbon or nitrogen, provided that only one of M and Q is nitrogen;

i is 2 or 3;

R_1 is (i) hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or a heterocyclo having a sulfur heteroatom or at least one of an oxygen and nitrogen heteroatom; or (ii) taken together with R_2 forms a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_2 is (i) hydrogen or lower alkyl or (ii) forms a heterocyclo with R_1 that is unsaturated or selected from 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine; or R_2 together with R_5 forms a five or six-membered heterocyclo;

R_3 is hydrogen, methyl, or $-CHR_{14}-(CH_2)_n-Z$, in which Z is selected from CH_3, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl;

R_5 is hydrogen, methyl, or ethyl; or R_5 together with R_2 forms a five or six membered heterocyclo;

R_6 is attached to any available carbon atom of ring Y and at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkoxy, amino, aminoalkyl, cyano, and halogen, provided that only one R_6 is selected from amino and aminoalkyl;

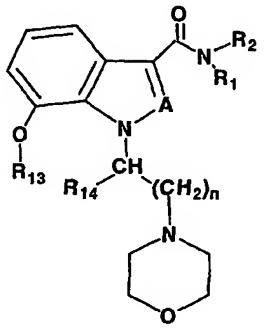
R_{6a} is hydrogen, alkyl, alkoxy, or OR_{13};

R_{13} is hydrogen, C_{1-6}alkyl, phenyl, benzyl, or the group $-CH_2-$ which bonds to R_{14} to form a six membered heterocyclo ring;

R_{14} is hydrogen or when R_{13} is $-CH_2-$, R_{14} is a bond; and

n is 0, 1, 2 or 3.

6. The method of claim 4, in which the cannabinoid receptor modulator has the formula:



or is a pharmaceutically acceptable salt or hydrate thereof, in which:

A is nitrogen or CR_5;

R_1 is alkyl, substituted alkyl, aryl, or cycloalkyl;

R_2 is hydrogen or lower alkyl;

R_5 is hydrogen, methyl, or ethyl;

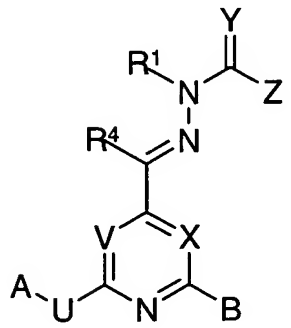
R_{13} is hydrogen, C_{1-6}alkyl, phenyl, benzyl, or the group $-CH_2-$ which bonds to R_{14} to form a six membered heterocyclo ring;

R_{14} is hydrogen or when R_{13} is $-CH_2-$, R_{14} is a bond; and

n is 1 or 2.

7. A compound having the formula:

under conditions sufficient to produce compounds having the formula:



wherein each of A, B, R^1, R^4, U, V, X Y and Z have the meanings provided above.

51. The method of Claim 50, wherein:

V is N and X is CH;

Y is O or S;

Z is NH_2;

R^1 is is selected from the group consisting of $(C_1$-$C_{10})$alkyl, $(C_1$-$C_{10})$heteroalkyl, heterocyclylalkyl, heteroaryl$(C_1$-$C_4)$alkyl and alkylene-$C(O)R^{11}$;

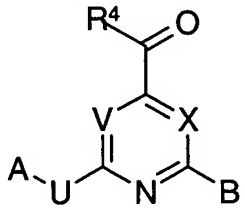
R^4 is H;

A is selected from the group consisting of $(C_1$-$C_{10})$alkyl, $(C_3$-$C_7)$cycloalkyl, $(C_1$-$C_{10})$heteroalkyl, heterocyclyl, heterocyclylalkyl, heterosubstituted cycloalkyl, aryl, aryl$(C_1$-$C_4)$alkyl and heteroaryl;

B is is selected from the group consisting of substituted or unsubstituted imidazoyl, substituted or unsubstituted thiazolyl and substituted or unsubstituted triazolyl; and

U is NH.

52. A compound having the formula:



wherein

one of either V or X is N and the other is $-CR_a$, or both V and X are $-CR_a$ (where each R_a is independently hydrogen, alkyl, cycloalkyl or cycloalkylalkyl;

R^4 is selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-alkyl, (C_2-C_6)alkenyl and (C_2-C_6)alkynyl;

A is selected from the group consisting of H, (C_1-C_{10})alkyl, (C_3-C_{10})alkenyl, (C_2-C_{10})alkynyl, (C_1-C_{10})heteroalkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-alkyl, (C_3-C_7) heterocyclylalkyl, heterocyclyl, heterosubstituted cycloalkyl, aryl, aryl(C_1-C_4)alkyl, aryl(C_1-C_4)heteroalkyl, heteroaryl, heteroaryl(C_1-C_4)alkyl ~~and~~ , heteroaryl(C_1-C_4)heteroalkyl and $R^aNHC(X)$- wherein R^a is (C_1-C_4)alkyl or aryl and X is O or S;

B is a substituted or unsubstituted five- or six-membered aromatic ring containing at least one nitrogen atom, and from 0 to 3 additional heteroatoms, wherein the B ring substituents are selected from the group consisting of halogen, CF_3, CF_3O, (C_1-C_6)alkyl, amino, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, cyano, nitro, sulfonamido, acyl, acylamino, and carboxamido;

U is NR^5, O or S; and,

R^5 is H or (C_1-C_6)alkyl.

53. The compound of Claim 52, wherein:

V is N and X is CH;

R^4 is H;

A is selected from the group consisting of (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, (C_1-C_{10})heteroalkyl, heterocyclyl, heterocyclylalkyl, heterosubstituted cycloalkyl, aryl, aryl(C_1-C_4)alkyl and heteroaryl;

B is is selected from the group consisting of substituted or unsubstituted imidazoyl, substituted or unsubstituted thiazolyl and substituted or unsubstituted triazolyl; and

U is NH.

* * * * * * *

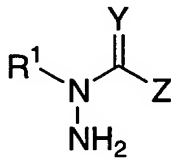
cycloalkyl, aryl, aryl(C_1-C_4)alkyl, aryl(C_1-C_4)heteroalkyl, heteroaryl, heteroaryl(C_1-C_4)alkyl and heteroaryl(C_1-C_4)heteroalkyl and R^aNHC(X)- wherein R^a is (C_1-C_4)alkyl or aryl and X is O or S;

B is a substituted or unsubstituted five- or six-membered aromatic ring containing at least one nitrogen atom, and from 0 to 3 additional heteroatoms, wherein the B ring substituents are selected from the group consisting of halogen, CF_3, CF_3O, (C_1-C_6)alkyl, amino, (C_1-C_6)alkylamino, di(C_1-C_6)alkylamino, cyano, nitro, sulfonamido, acyl, acylamino and carboxamido;

U is NR^5, O or S; and,

R^5 is H or (C_1-C_6)alkyl

with a compound having the formula:



wherein

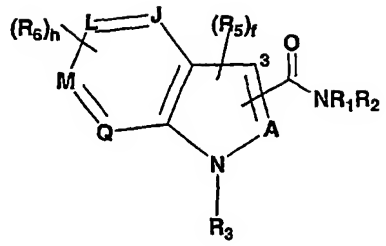
Y is selected from the group consisting of O, S and NR;

wherein R is selected from the group consisting of H, CN, NO_2, (C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-alkyl, (C_3-C_{10})alkenyl and (C_2-C_{10})alkynyl;

Z is selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-alkyl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl and $N(R^2)(R^3)$;

R^1 is selected from the group consisting of H, (C_1-C_{10})alkyl, (C_3-C_{10})alkenyl, (C_2-C_{10})alkynyl, (C_3-C_7)cycloalkyl, (C_3-C_7)cycloalkyl-alkyl, (C_1-C_{10})heteroalkyl, heterocyclylalkyl, heterocyclyl, aryl, aryl(C_1-C_4)alkyl, aryl(C_1-C_4)heteroalkyl, heteroaryl(C_1-C_4)alkyl, heteroaryl(C_1-C_4)heteroalkyl, –C(O)R^{11} or alkylene-C(O)R^{11}; and

R^2 and R^3 are each members independently selected from the group consisting of H, (C_1-C_{10})alkyl, (C_3-C_{10})alkenyl, (C_2-C_{10})alkynyl, (C_1-C_{10})heteroalkyl, (C_3-C_7)cycloalkyl, or (C_3-C_7)cycloalkyl-alkyl, or R^2 and R^3 can be combined to form a 5-7-membered heterocyclyl ring;



or a pharmaceutically acceptable salt or hydrate thereof, in which:

A is carbon or nitrogen; wherein when A is nitrogen, the group -C(=O)NR_1R_2 is attached to atom C-3 and R_5 does not exist; and when A is carbon, one of the group -C(=O)NR_1R_2 and R_5 is attached to A and the other of -C(=O)NR_1R_2 and R_5 is attached to atom C-3;

Q is nitrogen or CR_{6a} and J, L, and M are carbon or nitrogen, provided that only one of J, L, M and Q is nitrogen;

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, and heterocyclo, wherein said heterocyclo has for its heteroatom or heteroatoms sulfur or at least one of nitrogen and oxygen; or R_2 together with R_1 forms a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine; or R_2 together with R_5 forms a five or six-membered heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy; or forms a heterocyclo with R_{6a};

R_5 is attached to A or atom C-3 and is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkoxy, or heterocyclo; or R_5 together with R_2 forms a five to six membered heterocyclo;

R_6 at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, -C(=O)R_8, -CO_2R_8, -$S(O)_2NR_8R_{10}$, -C(=O)$N(R_8)O(R_9)$, -C(=O)NR_8R_9, and -OC(=O)R_{10}, provided only one of said R_6 groups is selected from amino and aminoalkyl;

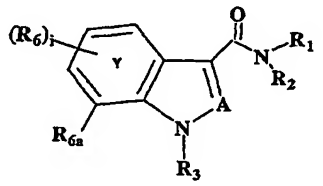
R_{6a} is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heterocyclo, hydroxy, alkoxy, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, $-C(=O)N(R_8)O(R_9)$, $-C(=O)NR_8R_9$, and $-OC(=O)R_{10}$; or forms a six-membered heterocyclo with R_3;

R_8 and R_9 at each occurrence selected independently are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, or heterocyclo; or R_8 and R_9 together form a three-to-eight membered heterocyclo; or R_8 with R_{10} forms a three-to-eight membered heterocyclo; and

R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8; and

u is 0, 1, 2 or 3.

8. The compound of claim 7 having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, in which:

A is CR_5 or nitrogen;

R_1 is alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or a heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen; or R_1 together with R_2 forms a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_2 is hydrogen, lower alkyl, or phenyl, or forms a heterocyclo with R_1 that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine,

and diazapine; or R_2 together with R_5 forms a five or six-membered heterocyclo;

R_3 is hydrogen, -(CHR_{14})-$(CH_2)_n$-Z, or –O-$(CH_2)_n$-Z;

R_5 is hydrogen, methyl, or ethyl; or R_5 together with R_2 forms five or six membered heterocyclo;

R_6 is attached to any available carbon atom of ring Y and at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkoxy, nitro, and halogen;

R_{6a} is hydrogen, alkyl, hydroxyalkyl, or alkoxy, or forms a six-membered heterocyclo with R_{14};

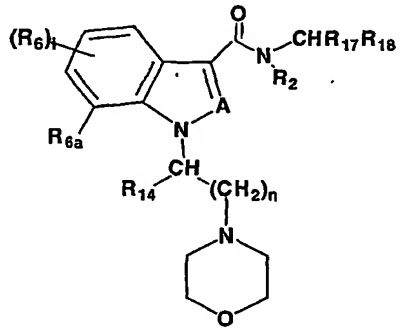
R_{14} is hydrogen or forms a six-membered heterocycle with R_{6a};

Z is hydrogen, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl;

i is 3; and

n is 0, 1, 2, 3, or 4.

9. The compound according to claim 8, having the formula:



or a pharmaceutically-acceptable salt thereof, in which

R_2 is hydrogen, methyl, ethyl, propyl, or phenyl, or forms a six-membered heterocyclo with R_5;

R_6 at each occurrence independent of each other R_6 is selected from hydrogen, C_{1-4}alkyl, alkoxy, nitro, and halogen;

R_{6a} is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, or C_{1-6}alkoxy, or forms a six-membered heterocyclo with R_{14};

R_{17} and R_{18} (i) independently of each other are $(CR_{21}R_{22})_s$-W, or (ii) together form aryl, heterocyclo, cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, aryl, cycloalkyl, and heteroaryl;

W at each occurrence is selected from hydrogen, alkyl, alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$, $-NR_{19}(C=O)R_{20}$, aryl, cycloalkyl, and heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;

R_{19} and R_{20} are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, and heterocyclo;

R_{21} and R_{22} are independently hydrogen, alkyl, hydroxy, or hydroxyalkyl;

n is 1 or 2; and

s is 0, 1, 2, 3 or 4.

10. The compound according to claim 9, or a pharmaceutically-acceptable salt or hydrate thereof, in which:

R_2 is hydrogen;

R_5 is hydrogen, methyl, or ethyl;

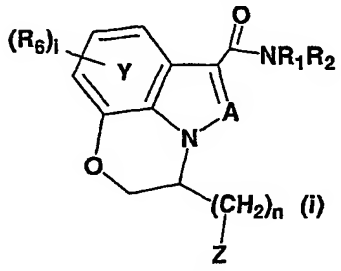
R_{14} is hydrogen;

R_{17} is benzyl and R_{18} is CO_2R_{19}; or R_{17} and R_{18} together form a five-to-eight membered cycloalkyl or bicycloalkyl optionally substituted with one to four C_{1-4}alkyl;

R_{19} is hydrogen or C_{1-4}alkyl; and

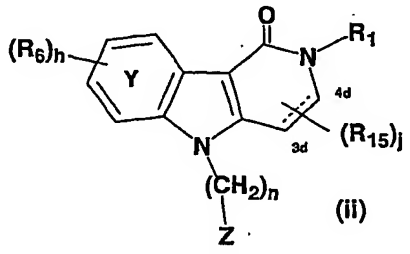
n is 1.

11. The compound of claim 7 having the formula (i) or (ii):



(i)

or



(ii)

or a pharmaceutically-acceptable salt or hydrate thereof, in which

A is CR_5 or nitrogen;

Z is hydrogen, alkoxy, amino, aminoalkyl, alkylamide, or heterocyclo;

R_1 is alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, or aryl;

R_2 is hydrogen, methyl, ethyl, or propyl;

R_5 is hydrogen, methyl, or ethyl;

R_6 is attached to any available carbon atom of ring Y and at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, alkoxy, nitro, and halogen;

R_{15} at each occurrence is hydrogen, halogen, alkyl, or cyano;

the bond linking atom C-3d and C-4d is a single or double bond;

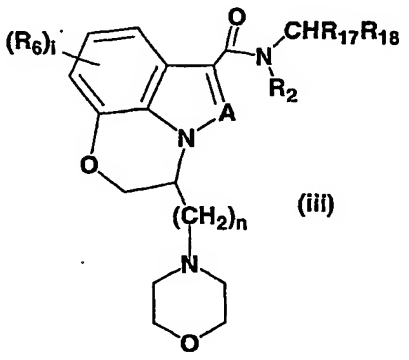
h is 4;

i is 3;

j is 2 or 4; and

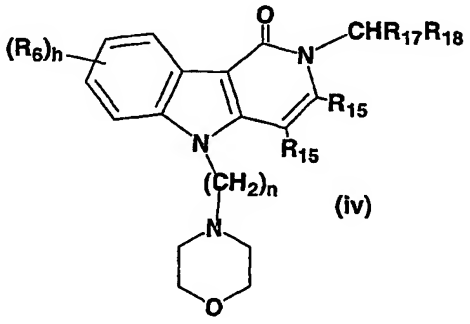
n is 1, 2, or 3.

12. The compound of claim 11 having the formula (iii) or (iv):



(iii)

or



(iv)

or a pharmaceutically-acceptable salt or hydrate thereof, in which

R_{17} and R_{18} (i) independently of each other are $(CR_{21}R_{22})_s$-W, or (ii) together form aryl, heterocyclo, cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, aryl, cycloalkyl, and heteroaryl;

W at each occurrence is selected from hydrogen, alkyl, alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$,

$-NR_{19}(C=O)R_{20}$, aryl, cycloalkyl, and heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen; and

R_{19} and R_{20} are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, and heterocyclo;

R_{21} and R_{22} are independently hydrogen, alkyl, hydroxy, or hydroxyalkyl;

n is 1 or 2; and

s is 0, 1, 2, 3 or 4.

13. The compound according to claim 7, selected from (i)

(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(2,2,6,6-tetramethylcyclohexyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide;

N-[[(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-L-tyrosine methyl ester;

(3R)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide;

N-[[(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]carbonyl]-L-phenylalanine methyl ester;

(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(2,2,6,6-tetramethylcyclohexyl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide;

(3S)-2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)pyrrolo[1,2,3-de]-1,4-benzoxazine-6-carboxamide;

2,3,4,5-Tetrahydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

N-[[5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

5-Fluoro-7-methoxy-N-(2-methoxyphenyl)-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide;

N-(2-Ethylphenyl)-5-fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide;

1-[[5-Fluoro-7-methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-1,2,3,4-tetrahydroquinoline;

5,7-Dimethoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

5-Fluoro-7-methoxy-2-methyl-N-[(1R)-1-methylpropyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide;

5-Fluoro-7-methoxy-2-methyl-1-[3-(4-morpholinyl)propyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

6,7-Dihydro-7-(4-morpholinylmethyl)-N-[(1S,2S)-1,3,3-trimethylbicyclo [2.2.1]heptan-2-yl]-5H-pyrazolo[5,1-b][1,3]oxazine-2-carboxamide;

(2S)-1-[[6,7-Dihydro-7-(4-morpholinylmethyl)-5H-pyrazolo[5,1-b][1,3] oxazin-2-yl]carbonyl]-2-(methoxymethyl)pyrrolidine;

N-[[7-Methoxy-2-methyl-1-[3-(4-morpholinyl)propyl]-1H-indol-3-yl] carbonyl]-L-phenylalanine methyl ester;

1-[2-(4-Morpholinyl)ethyl]-5-nitro-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrazole-3-carboxamide;

1-[2-(4-Morpholinyl)ethyl]-3-nitro-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrazole-5-carboxamide;

7-Methoxy-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-pentyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-[2-(4-piperidyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-1-(2-methoxyethyl)-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-(3-pyridinyl-methyl)-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-[3-(4-morpholinyl)propyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

1-[2-(Dimethylamino)ethyl]-7-methoxy-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-[2-(1-pyrrolidinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-1-[(4-methoxyphenyl)methyl]-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

1-(2-Cyclohexylethyl)-7-methoxy-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

1-[2-[Bis(1-methylethyl)amino]ethyl]-7-methoxy-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide

1-(2-Ethoxyethyl)-7-methoxy-2-methyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-[2-(1-methyl-2-pyrrolidinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-(2-phenoxyethyl)-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-1-[3-(4-methyl-1-piperazinyl)propyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-indole-3-carboxamide;

5-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrazole-3-carboxamide;

1-[2-(4-Morpholinyl)ethyl]-5-(pentyloxy)-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrazole-3-carboxamide;

(2S)-2-(Methoxymethyl)-1-[[1-[2-(4-morpholinyl)ethyl]-5-(pentyloxy)-1H-pyrazol-3-yl]carbonyl]pyrrolidine;

2,5-Dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-propyl-1H-pyrido[4,3-b]indol-1-one;

2-Cyclopentyl-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-2-(2-methoxyphenyl)-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-2-(2-methoxyethyl)-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(3R)-tetrahydro-3-furanyl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1R)-1-methyl-2-phenylethyl]-1H-pyrido[4,3-b]indol-1-one;

2-(2,3-Dihydro-1H-inden-1-yl)-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2-(Bicyclo[2.2.1]heptan-2-yl)-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-(3,3,5-trimethylcyclo-hexanyl)-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-3-methyl-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

2-[(2-Fluorophenyl)methyl]-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2-[(2,6-Dimethylphenyl)-methyl]-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1R,2R)-1,3,3-trimethylbicyclo[2.2.1]-heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

2,5-Dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

1,5-Dihydro-1-[2-(4-morpholinyl)ethyl]-5-[(1R,2R)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-4H-pyrido[3,2-c]pyridin-4-one;

1,5-Dihydro-5-[(2-methoxyphenyl)methyl]-1-[2-(4-morpholinyl)ethyl]-4H-pyrido[3,2-c]pyridin-4-one;

2,5-Dihydro-6-methoxy-5-(phenylmethyl)-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

5-Butyl-2,5-dihydro-6-methoxy-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

4-Methyl-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

4-Fluoro-2,5-dihydro-6-methoxy-5-[2-(4-morpholinyl)ethyl]-2-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrido[4,3-b]indol-1-one;

2-Methyl-1-[2-(4-morpholinyl)ethyl]-5-phenyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrrole-3-carboxamide;

2-Methyl-1-[2-(4-morpholinyl)ethyl]-4,5-diphenyl-N-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-1H-pyrrole-3-carboxamide;

1,5-Dihydro-1-[2-(4-morpholinyl)ethyl]-2-phenyl-5-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-4H-pyrido[3,2-c]pyridin-4-one;

1,5-Dihydro-1-[2-(4-morpholinyl)ethyl]-2,3-diphenyl-5-[(1S,2S)-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-4H-pyrido[3,2-c]pyridin-4-one;

7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-(2,2,6,6-tetramethylcyclohexyl)-1H-indazole-3-carboxamide;

7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-[(3R)-1-(phenylmethyl)-3-pyrrolidinyl]-1H-indazole-3-carboxamide;

7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-[(3S)-1-(phenylmethyl)-3-pyrrolidinyl]-1H-indazole-3-carboxamide;

7-Methoxy-N-[(1S)-1-(2-methyl-2H-tetrazol-5-yl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

N-[(1S)-1-(Aminocarbonyl)-2-phenylethyl]-7-methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

7-Methoxy-N-[(2-methoxyphenyl)methyl]-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

7-Methoxy-N-(2-methoxyphenyl)-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

7-Methoxy-N-(2-methoxy-5-methylphenyl)-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

N-(5-Chloro-2-methoxyphenyl)-7-methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

N-(4-Fluorophenyl)-7-methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

7-Methoxy-N-methyl-N-(3-methylphenyl)-1-[2-(4-morpholinyl)ethyl]-1H-indazole-3-carboxamide;

N-[[5-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[6-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[7-Hydroxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalaninamide;

N-[[2,7-Dimethyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-tyrosine methyl ester;

N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-3-methyl-L-valine methyl ester;

N^2-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-N,N-dimethyl-L-phenylalaninamide;

(1S)-N-[1-(Hydroxymethyl)-2-phenylethyl]-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide;

N-[[2-Methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethyl-bicyclo[2.2.1]heptan-2-yl)-1H-indole-3-carboxamide;

(αS)-α-[[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]amino]-2-thiophenepropanoic acid methyl ester;

N-[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-6-aza-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-L-phenylalanine methyl ester;

7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-indazol-3-carboxamide;

N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-R-amphetamide;

(αS)-α-[[[7-Methoxy-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]amino]-2-thiazolepropanoic acid methyl ester;

7-Methoxy-2-methyl-N-[(1S)-1-(3-methyl)-tetrazolyl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide;

7-Methoxy-2-methyl-N-[(1S)-1-(2-methyl)-tetrazolyl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-indole-3-carboxamide;

N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[7-Methoxy-1-[2-(4-morpholinyl)ethyl]-1H-indazol-3-yl]carbonyl]-1-naphthyl amide;

7-Methoxy-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-indole-3-carboxamide;

2-Methyl-1-[2-(4-morpholinyl)ethyl]-N-(1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl)-1H-pyrrole-3-carboxamide;

2,5-Dimethyl-N-[(1R)-1-methyl-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-pyrrole-3-carboxamide;

N-[[2,5-Dimethyl-1-[2-(4-morpholinyl)ethyl]-1H-pyrrol-3-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[2-Methyl-1-[2-(4-morpholinyl)ethyl]-1H-pyrrol-3-yl]carbonyl]-L-phenylalanine methyl ester;

2-Methyl-N-[(1S)-1-(3-methyl-1,2,4-oxadiazol-5-yl)-2-phenylethyl]-1-[2-(4-morpholinyl)ethyl]-1H-pyrrole-3-carboxamide;

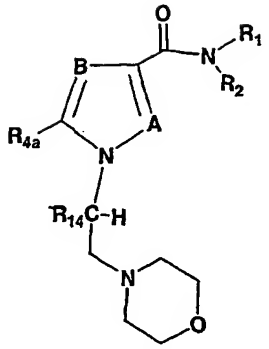
N-[[1-[2-(4-Morpholinyl)ethyl]-1H-imidazol-4-yl]carbonyl]-L-phenylalanine methyl ester;

N-[[1-(2-Phenoxyethyl)-1H-imidazol-4-yl]carbonyl]-L-phenylalanine methyl ester; and

N-[(1-Pentyl-1H-imidazol-4-yl)carbonyl]-L-phenylalanine methyl ester; and

(ii) a pharmaceutically-acceptable salt or hydrate thereof.

14. A compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, in which:

A is nitrogen or CR_5;

B is nitrogen or CR_{4b}, provided that A and B are not both nitrogen;

R_1 is $-CHR_{17}R_{18}$;

R_2 is hydrogen, lower alkyl, phenyl, or forms a five or six membered heterocyclo with R_5;

R_{4a} is hydrogen, alkyl, aryl, or OR_{13};

R_{4b} is hydrogen, alkyl, alkoxy, amino, cyano, halogen, or aryl;

R_5 is hydrogen, methyl or ethyl, or forms a heterocyclo with R_2;

R_{13} is hydrogen, C_{1-6}alkyl, phenyl, benzyl, or $-CH_2-$ which together with R_{14} forms a six membered heterocyclo ring;

R_{14} is hydrogen or when R_{13} is $-CH_2-$, a bond linked to R_{13};

R_{17} and R_{18} are (i) selected independently from hydrogen and $-(CH_2)_s-(CR_{21}R_{22})_v-(CH_2)_t-W$; or (ii) R_{17} and R_{18} together form cycloalkyl, aryl, or heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;

W at each occurrence is selected from CH_3, alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$, $-NR_{19}(C=O)R_{20}$, aryl, cycloalkyl, and heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;

R_{19} and R_{20} are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, and heterocyclo;

R_{21} and R_{22} are independently hydrogen, alkyl, hydroxy, or hydroxyalkyl;

s and *t* are 0, 1 or 2; and

v is 0 or 1.

15. The compound according to claim 14, or a pharmaceutically-acceptable salt thereof, in which

R_1 is $-CHR_{17}R_{18}$;

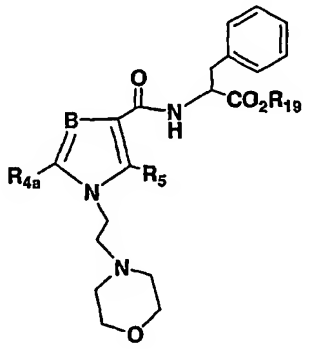
R_2 is hydrogen, methyl, ethyl, propyl, or phenyl;

R_{17} and R_{18} (i) independently of each other are $(CH_2)_s$-$(CR_{21}R_{22})_v$-$(CH_2)_t$-W, or (ii) together form a three-to-eight membered cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, aryl, cycloalkyl, and heteroaryl, or together form optionally substituted napthyl, tetrahydronapthyl, acenapthyl, dihydroindenyl, pyrazolyl, or benzodioxapinyl;

W at each occurrence is selected from $-CH_3$, C_{1-4}alkylthio, C_{1-4}alkoxy, hydroxy, cyano, $-CO_2H$, $-CO_2C_{1-4}$alkyl, $-C(=O)N(C_{1-4}alkyl)_2$, $-C(=O)NH(C_{1-4}$alkyl), -C(=O)NH(cycloalkyl), -C(=O)H, $-C(=O)NH_2$, $-C(=O)C_{1-4}$alkyl, $-C(=O)N(C_{1-4}alkyl)O(C_{1-4}$alkyl), $-NH(C=O)C_{1-4}$alkyl, $-N(C_{1-4}alkyl)$(phenyl), -NH(C=O)phenyl, phenyl, imidazole, biphenyl, diphenylC_{1-4}alkyl, pyridine, pyrrolidine, thiophene, pyrazole, imidazole, tetrazole, oxazole, oxadiazole, and napthyl, wherein said group W is optionally substituted with one to four C_{1-4}alkyl, hydroxy, halogen, cyano, C_{1-4}alkoxy, keto, trifluoromethyl, amino, acetylamino, five-or-six membered heterocyclo, three-to-eight membered cycloalkyl, benzyl, or aryl; and

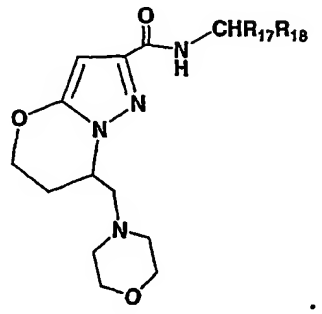
R_{21} and R_{22} are lower alkyl, hydroxy, or hydroxyalkyl.

16. The compound according to claim 14, or a pharmaceutically-acceptable salt thereof, having the formula:



in which B is N or CH; and R_{4a}, R_5, and R_{19} are independently hydrogen or C_{1-4}alkyl.

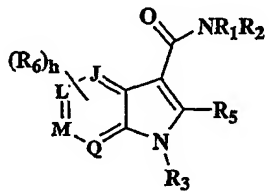
17. The compound according to claim 14, or a pharmaceutically-acceptable salt thereof, having the formula:



18. A pharmaceutical composition adapted for treating a respiratory disease or non-respiratory leukocyte-activation associated disease in a mammal comprising a therapeutically-effective amount of at least one cannabinoid receptor modulator according to claim 7 and a pharmaceutically-acceptable carrier or diluent.

19. A pharmaceutical composition for treating a respiratory disease or non-respiratory leukocyte-activation associated disease in a mammal comprising (i) one or more compounds according to claim 7; (ii) one or more second compounds effective for treating a leukocyte-activation associated disease in a mammal; and (iii) a pharmaceutically-acceptable carrier or diluent.

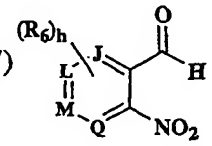
20. A process of preparing a compound according to claim 7 having the formula (Ij):

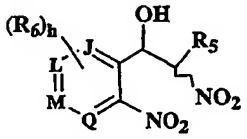


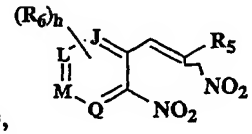
(Ij)

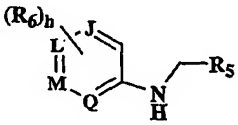
in which R_2 and R_5 are selected independently of each other, and when Q is CR_{6a}, R_3 and R_{6a} are selected independently of each other;

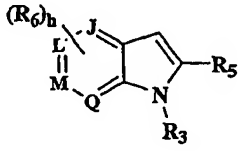
said process comprising:

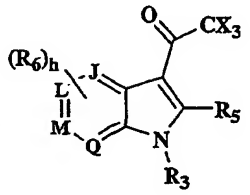
a) reacting compound (7)  (7) with a nitroalkyl in the presence of a halide salt and a crown ether to form a compound (7a),

 (7a) ;

b) reacting the compound (7a) with acetic anhydride and a fluorine-containing agent in the presence of 18-crown-6 to give a compound (7b),  (7b) ;

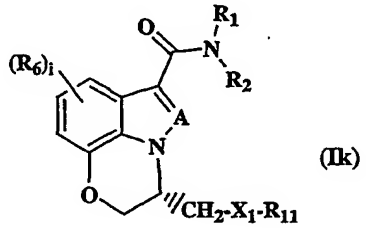
c) reducing the compound (7b) under hydrogenation conditions in a solvent to provide a compound (9),  (9) ;

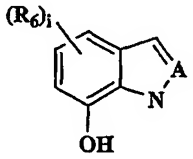
d) treating the compound (9) with an R_3-halide in the presence of a base and a solvent to form a compound (29),  (29)

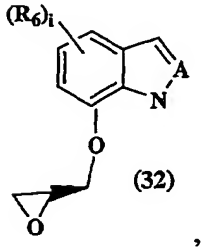
e) treating the compound (29) with trihaloacetyl halide optionally in the presence of a base and a solvent to give a compound (30),  (30),

wherein X is halide; and

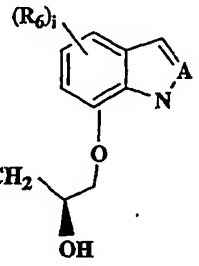
f) treating the compound (30) with an amine in the presence of a base to form the compound of formula (Ij).

21. A process of producing a compound according to claim 7 having the formula (Ik):  (Ik), wherein R_2 is selected independently of R_5, *i* is 3, and X_1-R_{11} is a nucleophile selected to define Z, said process comprising:

a) reacting a compound of formula (31)  (31)

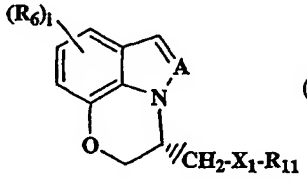
with (R)-(+)-glycidol under Mitsunobu conditions to give a compound (32),  (32),

b) reacting the compound (32) with a nucleophile R_{11}-X_1 (or R_{11}-X_1–H where H is hydrogen) to give a compound (33),



(33)

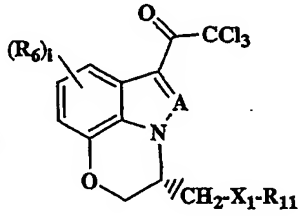
c) reacting the compound (33) under Mitsunobu conditions to give a compound (34),



(34)

;

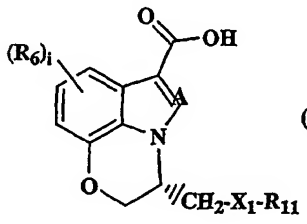
d) reacting the compound (34) with trihaloacetyl halide at a temperature of greater than 40°C to give a compound (35),



(35)

about

e) hydrolyzing the compound (35) under basic conditions to give a compound (36),

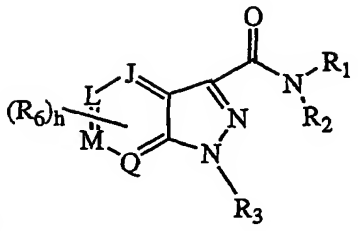


(36)

; and

f) reacting the compound (36) with an amine under amide bond coupling conditions to give the compound of formula (Ik).

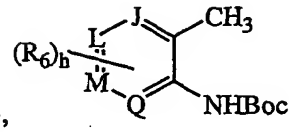
22. A process of producing a compound according to claim 7 having the formula (In):



(In)

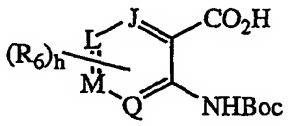
comprising:

a) reacting a compound of formula (37),



(37)

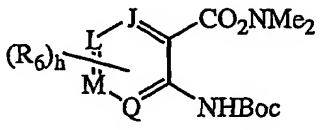
with an alkyl lithium and carbon dioxide to form a compound (38),



(38)

;

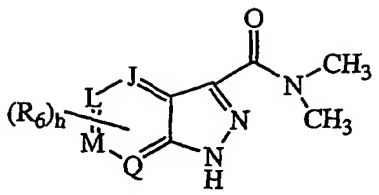
b) reacting the compound (38) with a dialkyl amine under amide bond conditions to form a compound (39),



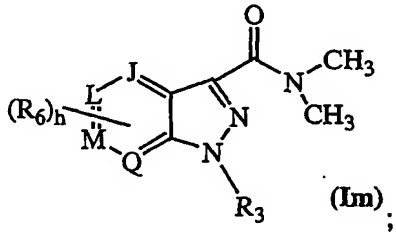
(39)

;

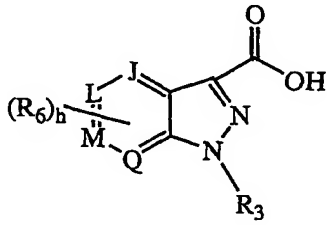
c) treating the compound (39) with a nitrite in aqueous acid at a temperature of about greater than 50°C to give a compound of formula (II),


(II)

d) treating the compound of formula (II) with R_3-X in the presence of a base to give a compound of formula (Im),


(Im);

e) hydrolyzing the compound of formula (Im) under aqueous basic conditions to produce a compound (40),


(40)

, and

f) reacting the compound (40) with an amine under amide bond coupling conditions to provide the compound of formula (In).

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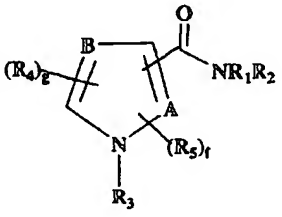
(54) Title: CANNABINOID RECEPTOR MODULATORS, THEIR PROCESSES OF PREPARATION, AND USE OF CANNABINOID RECEPTOR MODULATORS IN TREATING RESPIRATORY AND NON-RESPIRATORY DISEASES



(I)

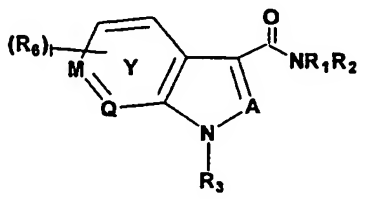
(57) Abstract: Use of a compound for treating a respiratory disease in a mammal wherein the compound is a cannabinoid receptor modulator is disclosed. Compounds useful as cannabinoid receptor modulators for treating respiratory and non-respiratory leukocyte-activation associated diseases comprise compounds of formula (I), in which A and B are nitrogen or carbon, provided only one of A and B is nitrogen; and R_1-R_6 are as defined in the specification, wherein R_2 with R_5 may form a ring, and/or two R_4 groups may form a six-membered aryl or heteroaryl ring, optionally having a substituent R_6 forming a ring with R_3.

AMENDED CLAIMS
[received by the International Bureau on 21 September 2001 (21.09.01);
original claims 5, 7, 8, 11 and 12 amended; remaining claims unchanged (7 pages)]

R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8; and

u is 0, 1, 2 or 3.

5. The method of claim 4, in which the cannabinoid receptor modulator has the formula:



or is a pharmaceutically acceptable salt or hydrate thereof, in which:

A is nitrogen or CR_5;

Q is nitrogen or CR_{6a} and M is carbon or nitrogen, provided that no more than one of M and Q is nitrogen;

i is 2 or 3;

R_1 is (i) hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or a heterocyclo having a sulfur heteroatom or at least one of an oxygen and nitrogen heteroatom; or (ii) taken together with R_2 forms a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_2 is (i) hydrogen or lower alkyl or (ii) forms a heterocyclo with R_1 that is unsaturated or selected from 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine; or R_2 together with R_5 forms a five or six-membered heterocyclo;

R_3 is hydrogen, methyl, or $-CHR_{14}-(CH_2)_n-Z$, in which Z is selected from CH_3, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl;

R_5 is hydrogen, methyl, or ethyl; or R_5 together with R_2 forms a five or six membered heterocyclo;

R_6 is attached to any available carbon atom of ring Y and at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkoxy, amino, aminoalkyl, cyano, and halogen, provided that no more than one R_6 is selected from amino and aminoalkyl;

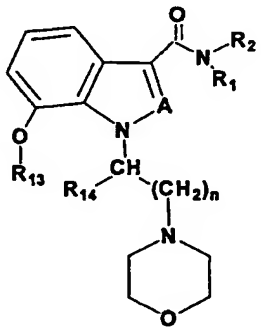
R_{6a} is hydrogen, alkyl, alkoxy, or OR_{13};

R_{13} is hydrogen, C_{1-6} alkyl, phenyl, benzyl, or the group $-CH_2-$ which bonds to R_{14} to form a six membered heterocyclo ring;

R_{14} is hydrogen or when R_{13} is $-CH_2-$, R_{14} is a bond; and

n is 0, 1, 2 or 3.

6. The method of claim 4, in which the cannabinoid receptor modulator has the formula:



or is a pharmaceutically acceptable salt or hydrate thereof, in which:

A is nitrogen or CR_5;

R_1 is alkyl, substituted alkyl, aryl, or cycloalkyl;

R_2 is hydrogen or lower alkyl;

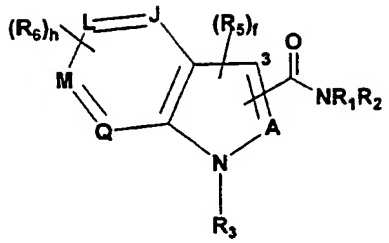
R_5 is hydrogen, methyl, or ethyl;

R_{13} is hydrogen, C_{1-6}alkyl, phenyl, benzyl, or the group $-CH_2-$ which bonds to R_{14} to form a six membered heterocyclo ring;

R_{14} is hydrogen or when R_{13} is $-CH_2-$, R_{14} is a bond; and

n is 1 or 2.

7. A compound having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, in which:

A is carbon or nitrogen; wherein when A is nitrogen, the group -C(=O)NR_1R_2 is attached to atom C-3 and R_5 does not exist; and when A is carbon, one of the group -C(=O)NR_1R_2 and R_5 is attached to A and the other of -C(=O)NR_1R_2 and R_5 is attached to atom C-3; f is O when A is nitrogen and f is 1 when A is carbon;

Q is nitrogen or CR_{6a} and J, L, and M are carbon or nitrogen, provided that no more than one of J, L, M and Q is nitrogen; h is 2 when one of J, L and M is nitrogen, and h is 3 when J, L and M are all carbon,

R_1 and R_2 are independently selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, and heterocyclo, wherein said heterocyclo has for its heteroatom or heteroatoms sulfur or at least one of nitrogen and oxygen; or R_2 together with R_1 forms a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine; or R_2 together with R_5 forms a five or six-membered heterocyclo;

R_3 is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, heterocyclo, or alkoxy; or forms a heterocyclo with R_{6a};

R_5 is attached to A or atom C-3 and is hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkoxy, or heterocyclo; or R_5 together with R_2 forms a five to six membered heterocyclo;

R_6 at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heterocyclo, hydroxy, alkoxy, amino, aminoalkyl, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, -C(=O)R_8, -CO_2R_8, -$S(O)_2NR_8R_{10}$, and -OC(=O)R_{10}, provided only one of said R_6 groups is selected from amino and aminoalkyl;

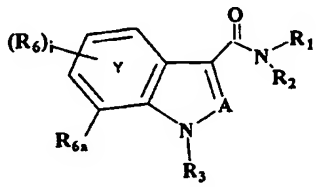
R_{6a} is selected from hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, cycloalkyl, heterocyclo, hydroxy, alkoxy, cyano, halogen, alkylamide, nitro, $NR_8C(=O)R_9$, $S(O)_uR_{10}$, $-C(=O)R_8$, $-CO_2R_8$, $-S(O)_2NR_8R_{10}$, and $-OC(=O)R_{10}$; or forms a six-membered heterocyclo with R_3;

R_8 and R_9 at each occurrence selected independently are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, aryl, or heterocyclo; or R_8 and R_9 together form a three-to-eight membered heterocyclo; or R_8 with R_{10} forms a three-to-eight membered heterocyclo; and

R_{10} at each occurrence independent of each other R_{10} is selected from alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl, or forms a heterocyclo with R_8; and

u is 0, 1, 2 or 3.

8. The compound of claim 7 having the formula:



or a pharmaceutically acceptable salt or hydrate thereof, in which:

A is CR_5 or nitrogen;

R_1 is alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, aryl, or a heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen; or R_1 together with R_2 forms a heterocyclo that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine, and diazapine;

R_2 is hydrogen, lower alkyl, or phenyl, or forms a heterocyclo with R_1 that is unsaturated or selected from optionally-substituted 1,2,3,4-tetrahydroquinoline, triazaspirodecane, morpholine, piperidine, pyrrolidine,

and diazapine; or R_2 together with R_5 forms a five or six-membered heterocyclo;

R_3 is hydrogen, -(CHR_{14})-$(CH_2)_n$-Z, or –O-$(CH_2)_n$-Z;

R_5 is hydrogen, methyl, or ethyl; or R_5 together with R_2 and the group -C(=O)N to which R_2 is attached forms a five or six membered heterocyclo;

R_6 is attached to any available carbon atom of ring Y and at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, substituted alkyl, alkoxy, nitro, and halogen;

R_{6a} is hydrogen, alkyl, hydroxyalkyl, or alkoxy, or forms a six-membered heterocyclo with R_{14};

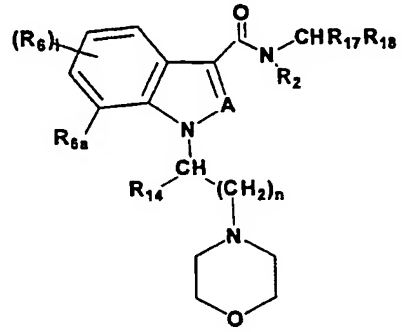
R_{14} is hydrogen or forms a six-membered heterocycle with R_{6a};

Z is hydrogen, CO_2H, amino, aminoalkyl, alkylamide, alkoxy, heterocyclo, aryl, or cycloalkyl;

h is 3; and

n is 0, 1, 2, 3, or 4.

9. The compound according to claim 8, having the formula:



or a pharmaceutically-acceptable salt thereof, in which

R_2 is hydrogen, methyl, ethyl, propyl, or phenyl, or forms a six-membered heterocyclo with R_5;

R_6 at each occurrence independent of each other R_6 is selected from hydrogen, C_{1-4}alkyl, alkoxy, nitro, and halogen;

R_{6a} is hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, or C_{1-6}alkoxy, or forms a six-membered heterocyclo with R_{14};

R_{17} and R_{18} (i) independently of each other are $(CR_{21}R_{22})_s$-W, or (ii) together form aryl, heterocyclo, cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, aryl, cycloalkyl, and heteroaryl;

W at each occurrence is selected from hydrogen, alkyl, alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$, $-NR_{19}(C=O)R_{20}$, aryl, cycloalkyl, and heterocyclo having as its heteroatom or heteroatoms sulfur or at least one of oxygen and nitrogen;

R_{19} and R_{20} are selected from hydrogen, alkyl, substituted alkyl, heterocycloalkyl, alkenyl, substituted alkenyl, cycloalkyl, aryl, and heterocyclo;

R_{21} and R_{22} are independently hydrogen, alkyl, hydroxy, or hydroxyalkyl;

n is 1 or 2; and

s is 0, 1, 2, 3 or 4.

10. The compound according to claim 9, or a pharmaceutically-acceptable salt or hydrate thereof, in which:

R_2 is hydrogen;

R_5 is hydrogen, methyl, or ethyl;

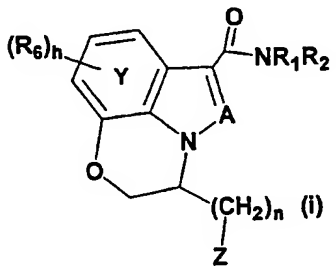
R_{14} is hydrogen;

R_{17} is benzyl and R_{18} is CO_2R_{19}; or R_{17} and R_{18} together form a five-to-eight membered cycloalkyl or bicycloalkyl optionally substituted with one to four C_{1-4}alkyl;

R_{19} is hydrogen or C_{1-4}alkyl; and

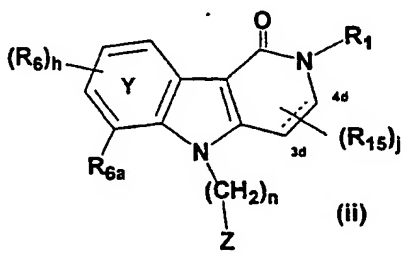
n is 1.

11. The compound of claim 8 having the formula (i) or (ii):



(i)

or



(ii)

or a pharmaceutically-acceptable salt or hydrate thereof, in which

A is CR_5 or nitrogen;

Z is hydrogen, alkoxy, amino, aminoalkyl, alkylamide, or heterocyclo;

R_1 is alkyl, substituted alkyl, heterocycloalkyl, cycloalkyl, or aryl;

R_2 is hydrogen, methyl, ethyl, or propyl;

R_5 is hydrogen, methyl, or ethyl;

R_6 is attached to any available carbon atom of ring Y and at each occurrence independent of each other R_6 is selected from hydrogen, alkyl, alkoxy, nitro, and halogen;

R_{6a} is selected from hydrogen, alkyl, hydroxyalkyl, and alkoxy,

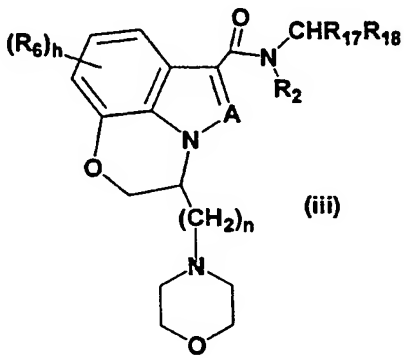
R_{15} at each occurrence is hydrogen, halogen, alkyl, or cyano;

the bond linking atom C-3d and C-4d is a single or double bond;

j is 2 or 4; and

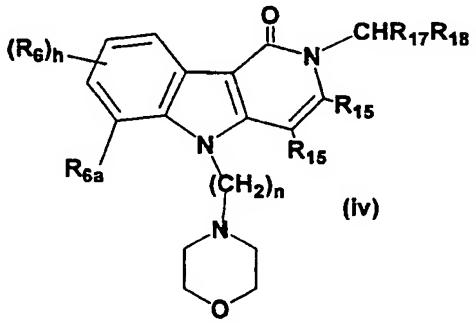
n is 1, 2, or 3.

12. The compound of claim 11 having the formula (iii) or (iv):



(iii)

or



(iv)

or a pharmaceutically-acceptable salt or hydrate thereof, in which

R_{17} and R_{18} (i) independently of each other are $(CR_{21}R_{22})_s$-W, or (ii) together form aryl, heterocyclo, cycloalkyl or bicycloalkyl optionally substituted with one to four groups selected from C_{1-4}alkyl, C_{1-4}alkoxy, aryl, cycloalkyl, and heteroaryl;

W at each occurrence is selected from hydrogen, alkyl, alkylamide, aminoalkyl, alkylthio, alkoxy, hydroxy, cyano, $-CO_2R_{19}$, $-C(=O)R_{19}$, $-C(=O)N(R_{19})O(R_{20})$,